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Sushma Sanganeria-Brady
Signature

Sushma Sanganeria-Brady
Typed or printed name of person signing Certificate

In re: application of: Qi Huang et al.
Application No.: 10/615,809
Filed: July 8, 2003
Title: SUBSTITUTED ANTHRANILIC AMIDE DERIVATIVES AND METHODS OF USE

Being faxed to Examiner – Joseph R. Kosack at facsimile number **1-571-273-8300** are the following documents:

1. This PTO/SB/97 Certificate of Transmission (1 page);
2. Transmittal (1 page); and
3. Appeal Brief (29 page submitted in duplicate).

Number of pages being transmitted: 60

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicants: **Qi Huang et al.** Docket No.: **A-817 (US)**

Application No: **10/615,809** Group Art Unit: **1626**

Filed: 07/08/2003 Examiner: Joseph R. Kosack

For: **SUBSTITUTED ANTHRANILIC AMIDE DERIVATIVES AND METHODS OF USE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

## TRANSMITTAL LETTER

Please find attached the following documents:

1. Appeal Brief ( 29 pages submitted in duplicate).

Please charge Deposit Account No. 01-0519 in the name of Amgen Inc. in the amount of $500.00. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No. 01-0519.

Respectfully submitted,

Customer No. 30,174
Amgen Inc.
1120 Veterans Boulevard
South San Francisco, CA 94080
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Fax: 650-837-9422

Ronald S. Hermenau
Reg. No. 34,620
Attorney for Applicants
Dated: February 14, 2007

### CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office, Fax No. (571) 273-8300, on the date appearing below.

April 16, 2007
Date

Sushma Sanganeria-Brady

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**Before the Board of Patent Appeals and Interferences**

| | |
|---|---|
| In re application of: **Qi Huang, et al.** | Attorney Docket No. **A-817 (US)** |
| Application No.: **10/615,809** | Art Unit No.: **1626** |
| Filed: **July 8, 2003** | Examiner: **Joseph R. Kosack** |
| Title: **SUBSTITUTED ANTHRANILIC AMIDE DERIVATIVES AND METHODS OF USE** | |

## APPEAL BRIEF

Mail Stop: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Applicants herein appeal from the Final Rejection mailed November 14, 2006, in which the Examiner rejected claims 1-3, 5-7, 9-11, 17, 19, 20, 23, 24, 29-31, 34 and 36 of the above-identified application, and objected to claim 32. Applicants filed a Notice of Appeal on February 14, 2007.

04/18/2007 RMEBRAHT 00000028 010519 10615809
01 FC:1402 500.00 DA

**CERTIFICATE OF FACSIMILE TRANSMISSION**

I hereby certify that this correspondence is being facsimile transmitted to Mail Stop: Appeal Brief-Patents, United States Patent and Trademark Office, (571) 273-8300, on the date shown below:

April 16, 2007 Sushma Sanganeria-Brady
Date Sushma Sanganeria Brady

## Real Party In Interest

The real party in interest is Amgen, Inc.

## Related Appeals And Interferences

Appellants are aware of no other prior or pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

## Status Of Claims

- Claims 5-7, 30, 31 and 34 stand rejected under 35 U.S.C. § 103.
- Claims 1, 2, 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32, 34 and 36 are objected to.
- Claims 3, 4, 8, 9, 12-16, 18, 21, 22, 25-28, 33 and 35 have been canceled.
- Claims 37-45 have been canceled as being drawn to an unelected invention group — but are properly subject to rejoinder

## Status Of Amendments

As indicated in the Advisory Action (Form PTOL-303, section 7) Appellants' proposed amendments submitted in response to the Final Action have been entered.

## Summary Of Claimed Subject Matter

The present application claims compounds having inhibitory kinase activity (such as VEGF/KDR inhibitory activity) and are thus potentially useful in treating cancer and angiogenisis (see specification at page 26 line 4 to page 30 line 31). Specifically, the specification discloses compounds of Formula I (see specification at page 6 line 4, to

page 15, line 5), as well as compounds of Formula I' (see specification at page 15, line 6, to page 24, line13). Specific compounds of particular interest are identified in the specification at page 24, line 14 to page 26, line 2.

Compounds of Formula I are claimed in independent claim 1 and dependent claim 36. Compounds of Formula I' are claimed in independent claim 2 and dependent claims 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32 and 34.

## Grounds Of Rejection To Be Reviewed On Appeal

(1) The Objection to claims 1, 2, 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32, 34 and 36 is based on an assertion that the claims contain non-elected subject matter. However, an intelligible explanation of this objection has never been clearly set forth. In the Final Action, the Examiner asserted that non-elected subject matter remained within the scope of variable $R^2$ (see Final Action at page 2 lines 15-16, and page 4 lines 1-3). However, as Appellants pointed out in their response to the Final Action, a restriction requirement directed to the scope of variable $R^2$ had never been issued. Thus Appellants requested that the Examiner clarify the nature of the objection (see Response to Final Action at page 15 lines 7-10). The Advisory Action fails to provide any clarification.

(2) Claims 5-7 and 9 stand rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819), Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

(3) Claim 31 stands rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

(4) Claims 30 and 34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176) and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

## Argument

### I. The Entirety of Non-Elected Subject Matter Has Been Removed From the Claims On Appeal

The Examiner objects to claims 1, 2, 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32, 34 and 36 on the asserted basis that the claims contain non-elected subject matter. However, an intelligible explanation of this objection has never been clearly set forth. In the Final Action, the Examiner asserted that non-elected subject matter remained within the scope of variable $R^2$ (see Final Action at page 2 lines 15-16, and page 4 lines 1-3). However, as Appellants pointed out in their response to the Final Action, a restriction requirement directed to the scope of variable $R^2$ had never been issued. Thus Appellants requested that the Examiner clarify the nature of the objection (see Response to Final Action at page 15 lines 7-10). The Advisory Action fails to elaborate on the nature of the objection

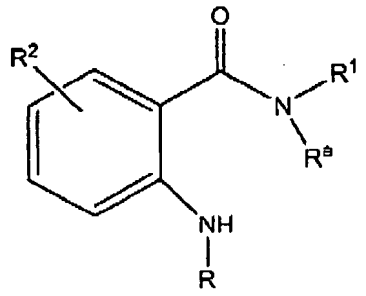
The Examiner's first Restriction Requirement is set forth in the Office Action mailed 12/7/05, in which the Examiner restricted the claimed subject matter between the following two Invention Groups (see 12/7/05 Office Action at page 2 lines 3-17):

I. Claims 1-36, drawn to compounds of Formula I, classified in various subclasses of class 514, 540, 544, 546 548 and 549.

II. Claims 37-45, drawn to drawn to [sic] methods of use of compounds of Formula I, classified in various subclasses of class 514, 540, 544, 546 548 and 549.

The Examiner additionally required that Appellants elect a single compound (see 12/7/05 Office Action at page 3 line 5 to page 6 line 12): In the next Office Action (mailed 4/13/06) the Examiner stated that:

"Pursuant to Applicant's election of species, the scope of the invention will be limited to the following substitutions of the base structure




where:

- R is $-(CH_2)_1-R^3$;
- $R^3$ is a 6 membered ring with ring members consisting of only carbon and nitrogen, optionally substituted as defined, optionally unsaturated as defined;
- All other substituents are as defined."

(4/13/06 Office Action at page 2 line 15 to page 3 line 4)

In response to this Office Action Appellants (1) argued that the proposed restriction of variable $R^3$ was improper as it employed limitation language that found no support in the specification (Appellants additionally proposed that a limitation of $R^3$ to the term "substituted or unsubstituted 5-6 membered heterocyclyl" would be more appropriate); (2) amended the claims to limit the definition of R to $-(CH_2)_1-R^3$; and (3) amended the claims to limit the definition of $R^3$ to "substituted or unsubstituted 5-6 membered heterocyclyl" (See Response mailed 8/11/06 and Response mailed 8/22/06). Appellants subsequently canceled claims 37-45, which were drawn to unelected Invention Group II — subject to the right to rejoinder (see Response to Final Office Action mailed 1/19/07 pages 14-15).

According to the Final Office Action, the Examiner asserts that the claims on appeal retain unelected subject matter within the scope of variable $R^2$. Yet, as shown

above, the Examiner never issued a restriction directed at the scope of variable $R^2$. Appellants' request for clarification on this matter remains unanswered.

While a restriction requirement directed to the scope of $R^2$ was never made, the Examiner did purport to restrict the scope of variables R and $R^3$, as discussed previously above (see 4/13/06 Office Action at page 2 line 15 to page 3 line 4). To the extent that the objection is actually based on a perceived requirement that — in order to remove non-elected subject matter — variable $R^3$ must be "*restricted*" to read: "$R^3$ is a 6-membered ring with ring members consisting of only carbon and nitrogen" such a requirement would be improper. In response to the Final Office Action, Appellants petitioned the Commissioner to Withdraw the Finality of the Office Action, asserting that the proposed restriction of variable $R^3$ was improper." In denying Appellants' petition the Commissioner explained: "The examiner's statement which appears to set a limit on the scope of the claims to be examined was meant to inform applicants of the *scope of the search* pertaining to the claims, **not limit the claim scope**." (3/16/07 PETITION DECISION at page 2 lines 24-27) (emphasis added).

Based on the above set of facts, Appellants assert that the entirety of non-elected subject matter has already been removed from the claims pending on appeal, and that the objection to claims 1, 2, 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32, 34 and 36 is improper.

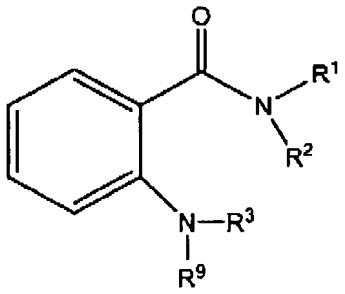
## II. The Examiner Has Failed To Establish A Prima Facie Case Of Obviousness In Relation To Claims 5-7 and 9

The Examiner has rejected claims 5-7 and 9 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819), Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137)*.

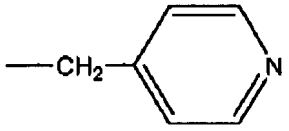
* Appellants question the inclusion of judicial decisions, such as In re Wood, as prior art references. While the holdings of judicial precedent can certainly be relied upon to support the underlying rationale of a rejection, the judicial decision itself does not appear to be properly categorized as "prior art".

Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 5 line 7, to page 7 line 12. Specifically, in attempting to support the rejection the Examiner notes that examples 2.39 and 2.56 of Huth et al. disclose compounds of the formula



where $R^2$ and $R^9$ are hydrogen, $R^3$ is



, and $R^1$ is indol-5-yl, or 4-chloropyridyl. Then the Examiner asserts that:

> "Patani et al. teach ring replacements of NH for $CH_2$ in aromatic and aliphatic rings. See pages 3158-3159. This would make the 5-yl and 6-yl indoles, as well as quinoline/isoquinoline, equivalent structures."

(Final Office Action at page 6 lines 12-14). The Examiner then proceeds to assert that:

> "Fotouhi et al. teach that substituting and [sic] 2,3-dihydro-1H-indole for indole give [sic] molecules with the same utility and comparable activities. See Example 315 on page 109, Example 38 on page 110, and the activities on page 136, column 2."

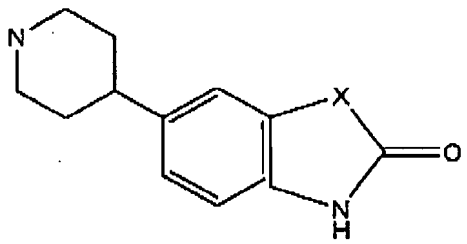
(Final Office Action at page 6 lines 15-17). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teachings of both Patani and Fotouhi far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that

***any*** and all "replacements of NH for $CH_2$ in aromatic and aliphatic rings"† will ***always*** provide "equivalent" structures, with "equivalent" properties relative to ***any and all*** biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad over-arching trends across diverse scaffolds and biologic targets, as a vain attempt in oversimplificaiton.

The Examiner's ultimate conclusion that Patani et all establish the equivalency of all 5-yl and 6-yl indoles under all circumstances is not even supported by the cited text of the reference (i..e., page 3158-3159). A review of the actually cited pages reveals a disclosure of 2 separate chemical scaffolds that both employ certain **5-yl** indolinone-type fragments (see e.g., Figure 34 (compound 52), and Figure 36). Each of these compound is distinct in both structure and chemical activity.

The first cited scaffold in Patani (Figure 34, compound 52) discloses a genus of **PDE III modulators** of the following formula::




X = $CH_2$, NH

This genus covers both

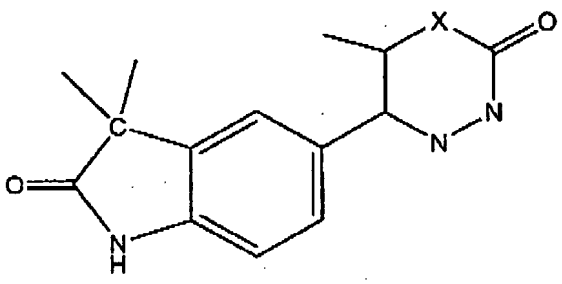
(1) **piperadin-5-yl**, 2,3-dihydro benzimidazol**ones**; and

(2) **piperadin-5-yl**, indoline -2-**one**

The cited scaffold thus encompasses only **5-yl** substituted 2,3-dihydrobenzimidazol**ones**/ or indolin**ones**

† Appellants note this NH could not be substituted with $CH_2$ in aromatic systems without violating rules of valancy.

The second cited scaffold in Patani (Figure 36, compound 54) disclose a genus of **Cardiotonic agents** of the following formula:




Like the previously cited scaffold, this second scaffold also encompasses only **5-yl** substitied 2,3-dihydrobenzimidaz**olones**/ or indolin**ones**

As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

- In making the broad conclusion the Examiner apparently sees fit to discount any activity effects that might be attributable to the differing specific substituents at the 5 position of the cited scaffolds in Patani.
- The cited compounds are all 5-yl substituted indolin**one** compounds. The Examiner does not provide any rational for the implicit equation of indoles and indolinones.
- Contrary to the Examiner's position, the cited reference does not disclose any purported equivalency between either 5-yl or 6-yl indoles. Indeed, the reverence only discloses 5-yl substituted indolinones. How the Examiner now draws a conclusion as to the universal equivalency of any and all corresponding 6-yl isomers, is beyond Appellants comprehension.
- The Examiner does not explain how Patani's disclosure of certain PDE III modulators in Figure 34, and other structurally distinct Cardiotonic agents in Figure 36, would lead any person of skill in

> the art to reasonably expect that certain fragments of the scaffold could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

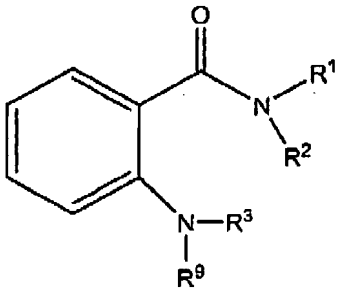
Moreover, the Examiner has not explained how a person of skill in the art, reviewing Fotouhi's disclosure (which relates to ICAM inhibitors of a structurally distinct scaffold), would conclude that the substitution of 2,3, dihydro-1-H indole for indole -- on the completely different kinase inhibitor scaffold covered by the claims on appeal – would be expected to yield compounds of similar properties. The Advisory Action indicates that this rejection has been maintained because:

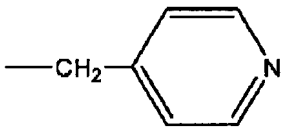
> "Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

**First:** Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets that VEGF/KDR (e.g., PDE III modulators, Cardiotonic agents and ICAM inhibitors)

## III. The Examiner Has Failed To Establish A Prima Facie Case Of Obviousness In Relation To Claim 31

The Examiner has rejected claim 31 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 10 line 3, to page 11 line 12. Specifically, in attempting to support the rejection the Examiner notes that example 2.56 of Huth et al. discloses a compound of the formula 

where $R^2$ and $R^9$ are hydrogen, $R^3$ is 

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(Final Office Action at page 10 lines 17-19). The Examiner then proceeds to assert that:

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(Final Office Action at page 11 lines 1-3). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teachings of both Patani and Fotouhi far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that ***any*** and all "replacements of NH for $CH_2$ in aromatic and aliphatic rings" will ***always*** provide "equivalent" structures, with "equivalent" properties relative to ***any and all*** biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad over-

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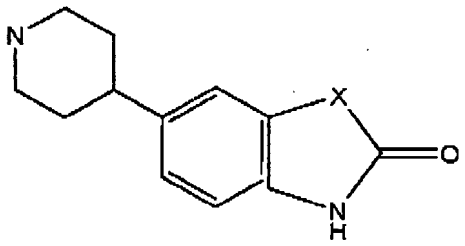


$X = CH_2, NH$

This genus covers both

(1) **piperadin-5-yl**, 2,3-dihydro benzimidazol**ones**; and

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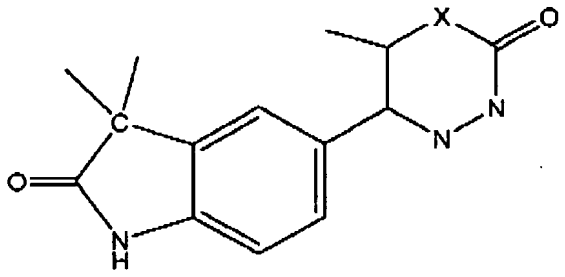


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As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

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- The Examiner does not explain how Patani's disclosure of certain PDE III modulators in Figure 34, and other structurally distinct Cardiotonic agents in Figure 36, would lead any person of skill in the art to reasonably expect that certain fragments of the scaffold could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

Moreover, the Examiner has not explained how a person of skill in the art, reviewing Fotouhi's disclosure (which relates to ICAM inhibitors of a structurally distinct scaffold), would conclude that the substitution of 2,3, dihydro-1-H indole for indole -- on the completely different kinase inhibitor scaffold covered by the claims on appeal -- would be expected to yield compounds of similar properties. The Advisory Action indicates that this rejection has been maintained because:

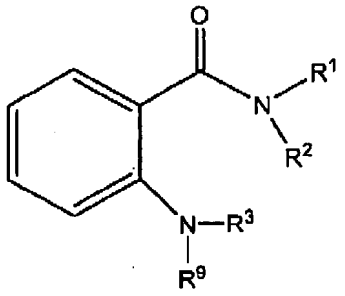
> "Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

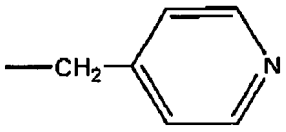
**First:** Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets that VEGF/KDR (e.g., PDE III modulators, Cardiotonic agents and ICAM inhibitors)

## IV. The Examiner Has Failed To Establish A Prima Facie Case Of Obviousness In Relation To Claims 30 and 34

The Examiner has rejected claim 30 and 34 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176) and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 8 line 11, to page 9 line 19. Specifically, in attempting to

support the rejection the Examiner notes that example 2.49 of Huth et al. discloses a compound of the formula 


where $R^2$ and $R^9$ are hydrogen, $R^3$ is 

, and $R^1$ is 7-1,2,3,4-tetrahydroquinolyl. Then the Examiner asserts that:

> "Patani et al. teach ring replacements of NH for $CH_2$ in aromatic and aliphatic rings. See pages 3158-3159. This would make pyridine/pyrimidine, as well as quinoline/isoquinoline equivalent structures."

(Final Office Action at page 9 lines 9-11). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teaching of both Patani far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that ***any*** and all "replacements of NH for $CH_2$ in aromatic and aliphatic rings" will ***always*** provide "equivalent" structures, with "equivalent" properties relative to ***any and all*** biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad over-arching trends across diverse scaffolds and biologic targets, as a vain attempt in oversimplificaiton.

The Examiner's ultimate conclusion that Patani et all establish the equivalency of all pyridine/pyrimidine and quinoline/isoquinoline under all circumstances is not even supported by the cited text of the reference (i..e., page 3158-3159). A review of the

actually cited pages reveals that (1) while some diverse scaffolds do employ pyridine fragments no chemical scaffolds are disclosed that employ pyrimidine fragments; and (2) while one scaffold discloses a specific antibacterial scaffold employing certain quinol**one**.and isoquinol**one** fragments, the references discloses no scaffolds encompassing quinol**ine** and isoquinol**ine** fragments. How the Examiner makes the logical leap establishing the equivalency of quinolones/quinolines and isoquinolones/isoquinonlins, is beyond Appellants' comprehension.

As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

- In making the broad conclusion the Examiner apparently sees fit to discount any activity effects that might be attributable to the differing specific substituents required in the cited scaffolds in Patani.
- The cited compound only disclose specific quinolone and isoquinolone compounds. The Examiner does not provide any rational for the implicit equation of these compounds to the structurally distinct quinoline and isoquinoline compounds covered in the claims pending on appeal.
- The Examiner does not explain how Patani's discosure of certain antibacterial quinolones and isoquinolones, would lead any person of skill in the art to reasonably expect that quinoline and isoquinoline fragments employed in the distinct the scaffold covered in the claims on appeal could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

The Advisory Action indicates that this rejection has been maintained because:

> "Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

**First:** Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets that VEGF/KDR (e.g. antibacterial agents)

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> "Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

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## V. The Teaching of Patani

Applicants respectfully submit that the Examiner has interpreted the teaching of Patani et al. far to broadly, and that a fair consideration of this reference does not actually provide anywhere near the absolute concrete guidance on equivalency that has been proposed by the Examiner. Indeed, a review of the pages of Patani et al. specifically cited by Examiner reveals that this disclosure does not even encompass topics such as the substitution of pyrimidine for pyridine, or the substitution of isoquinoline for quinoline. Rather, these pages disclose, *at best*, that:

(1) in relation to antihistamine effect, certain pyridines and phenyls can be employed to obtain active compounds (see Figure 31 at p. 3158),

(2) in relation to antibacterial effect, certain quinilones and isoquinolones can be employed to obtain active compounds (see Figure 38 at p. 3159); and

(3) in relation to certain PDE III modulator scaffolds certain 2,3-dihydrobenzimidazolone fragments can be substituted for indolinone fragments.

The other ring systems discussed at pages 3158-3159 of Patani et al., do not even approach structural similarity between pyridines/pyrimidones or quinolines/isoquinolines. The Examiner's belief that this disclosure of Patani et al. clearly establishes that any substitution of N for CH in any aromatic systems (or NH for $CH_2$ in any non-aromatic systems) will always result in compounds of equivalent activity in all targets, is simply an overreaching interpretation that is not supported by the disclosure itself. Indeed Patani et al. specifically note that:

- "The concept of bioisoseterism is often considered to be qualitative and intuitive." (Patani et al. at page 3147), rather than the facile, precise, all-encompassing generalizations than have been put forth by the Examiner.

- The substitutions discussed in the reference only represent *potential* for producing compounds of similar activity. (See page 3148: "Thus, an additional objective of this review was to demonstrate *the opportunities* that one has in employing bioisosteres" (emphasis added); and "Bioisosteric replacements of functional groups ... have enhanced *the potential* for the successful development of new clinical agents" (emphasis added); See also page 3158: "Classical isosteric substitutions when applied within ring systems result in different heterocyclic analogues which *can be* effective bioisoteres."). Thus, it is clear that Patani et al. do not

purport to endorse the type of broad interpretation that has been set forth by the Examiner, in an attempt to support this rejection. At best, Patani et al. provide a suggestion **to try** isosteric substitutions in order to find bioisosteric equivalents in relation to certain targets. Patani, et al. do not even attempt to suggest that such substitutions will always work in any target at issue.

The Examiner's extremely overbroad interpretation of Patani et al. represents the very foundation of the obviousness rejections. The failure of the Patani reference to actually suggest the propositions set forth by the Examiner, dooms the remainder of the analysis to failure.

## CONCLUSION

Based on the above observations and arguments, Appellants respectfully request that the Board reverse the Objections and Rejections that have been set forth in the Advisory Action and remand the case to the Examiner to pass the claims to allowance.

Respectfully submitted,

Dated: April 16, 2007

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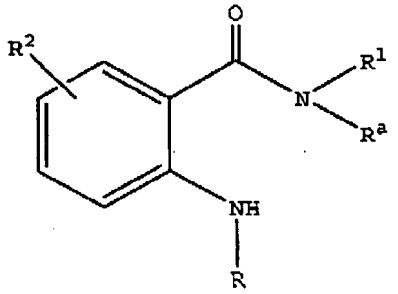
## CLAIMS APPENDIX

1. A compound of Formula I



I

wherein R is

$-(CH_2)_1-R^3$;

wherein $R^1$ is selected from 1,2-dihydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, 2,3-dihydro-1H-indolyl, and 1,4-benzodioxanyl; wherein $R^1$ is unsubstituted or substituted with one or more substituents selected from bromo, chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, oxo, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-

butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy, methoxy and ethoxy;

wherein $R^2$ is one or more substituents independently selected from

H,

halo,

hydroxy,

amino,

$C_{1-6}$-alkyl,

$C_{1-6}$-haloalkyl,

$C_{1-6}$-alkoxy,

$C_{1-2}$-alkylamino,

aminosulfonyl,

$C_{3-6}$-cycloalkyl,

cyano,

$C_{1-2}$-hydroxyalkyl,

nitro,

$C_{2-3}$-alkenyl,

$C_{2-3}$-alkynyl,

$C_{1-6}$-haloalkoxy,

$C_{1-6}$-carboxyalkyl,

4-6-membered heterocyclyl-$C_{1-6}$-alkylamino,

unsubstituted or substituted phenyl and

unsubstituted or substituted 4-6 membered heterocyclyl;

wherein $R^3$ is substituted or unsubstituted 5-6 membered heterocyclyl; wherein substituted $R^3$ is substituted with one or more substituents independently selected from halo, $-OR^4$, $-SR^4$, $-SO_2R^4$, $-CO_2R^4$, $-CONR^4R^4$, $-COR^4$, $-NR^4R^4$, $-SO_2NR^4R^4$, $-NR^4C(O)OR^4$, $-NR^4C(O)R^4$, cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, lower alkyl substituted with $R^2$, cyano, nitro, lower alkenyl and lower alkynyl;

wherein $R^4$ is independently selected from H, lower alkyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted $C_3$-$C_6$ cycloalkyl, phenyl-$C_{1-6}$-alkyl, optionally substituted 4-6 membered heterocyclyl-$C_{1-6}$-alkyl, and lower haloalkyl;

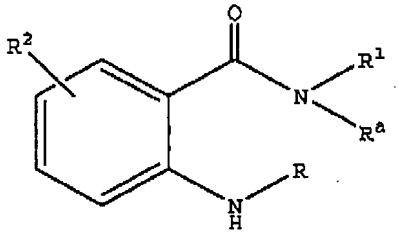
wherein $R^5$ is selected from H, $C_{1-3}$-alkyl, optionally substituted phenyl, optionally substituted phenyl-$C_{1-3}$-alkyl, 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-$C_1$-$C_3$-alkyl, $C_{1-3}$-alkoxy-$C_{1-2}$-alkyl and $C_{1-3}$-alkoxy-$C_{1-3}$-alkoxy-$C_{1-3}$-alkyl;

wherein $R^a$ is selected from H and $C_{1-2}$-alkyl; and

wherein $R^b$ and $R^c$ are independently selected from H and $C_{1-2}$-haloalkyl;

and pharmaceutically acceptable salts thereof.

2. A compound of Formula I'



I'

wherein R is

$-(CH_2)_1-R^3$;

wherein $R^1$ is selected from 1,2-dihydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, 2,3-dihydro-1H-indolyl, and 1,4-benzodioxanyl; wherein $R^1$ is unsubstituted or substituted with one or more substituents selected from bromo, chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, oxo, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-

methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy, methoxy and ethoxy;;

wherein $R^2$ is one or more substituents independently selected from

H,

halo,

hydroxy,

amino,

$C_{1-6}$-alkyl,

$C_{1-6}$-haloalkyl,

$C_{1-6}$-alkoxy,

$C_{1-2}$-alkylamino,

aminosulfonyl,
$C_{3-6}$-cycloalkyl,
cyano,
$C_{1-2}$-hydroxyalkyl,
nitro,
$C_{2-3}$-alkenyl,
$C_{2-3}$-alkynyl,
$C_{1-6}$-haloalkoxy,
$C_{1-6}$-carboxyalkyl,
4-6-membered heterocyclyl-$C_{1-6}$-alkylamino,
unsubstituted or substituted phenyl and
unsubstituted or substituted 4-6 membered heterocyclyl;

wherein $R^3$ is substituted or unsubstituted 5-6 membered heterocyclyl; wherein substituted $R^3$ is substituted with one or more substituents independently selected from halo, $-OR^4$, $-SR^4$, $-SO_2R^4$, $-CO_2R^4$, $-CONR^4R^4$, $-COR^4$, $-NR^4R^4$, $-SO_2NR^4R^4$, $-NR^4C(O)OR^4$, $-NR^4C(O)R^4$, cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, lower alkyl substituted with $R^6$, cyano, nitro, lower alkenyl and lower alkynyl;

wherein $R^4$ is independently selected from H, lower alkyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted $C_3$-$C_6$ cycloalkyl, phenyl-$C_{1-6}$-alkyl, optionally substituted 4-6 membered heterocyclyl-$C_{1-6}$-alkyl, and lower haloalkyl;

wherein $R^5$ is selected from H, $C_{1-3}$-alkyl, optionally substituted phenyl, optionally substituted phenyl-$C_{1-3}$-alkyl, 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-$C_1$-$C_3$-alkyl, $C_{1-3}$-alkoxy-$C_{1-2}$-alkyl and $C_{1-3}$-alkoxy-$C_{1-3}$-alkoxy-$C_{1-3}$-alkyl;

wherein $R^6$ is selected from H, halo, hydroxy, amino, $C_{1-6}$-alkoxy, $C_{1-2}$-alkylamino, aminosulfonyl, $C_{3-6}$-cycloalkyl, cyano, nitro, $C_{1-6}$-haloalkoxy, carboxy, 4-6-membered heterocyclyl-$C_{1-6}$-alkylamino, unsubstituted or substituted phenyl and unsubstituted or substituted 4-6 membered heterocyclyl;

wherein $R^a$ is selected from H and $C_{1-2}$-alkyl; and

wherein $R^b$ and $R^c$ are independently selected from H and $C_{1-2}$-haloalkyl;

and pharmaceutically acceptable salts thereof.

3. (Canceled)

4. (Canceled)

5. Compound of Claim 2 wherein $R^1$ is selected from 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinol-7-yl, 2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinol-7-yl, 2,3-dihydro-1H-indolyl, 3,3-dimethyl-2,3-dihydro-1H-indol-6-yl, 1-ethyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl, and 1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl; and pharmaceutically acceptable salts thereof.

6. Compound of Claim 5 wherein $R^1$ is 3,3-dimethyl-2,3-dihydro-1H-indol-6-yl; and pharmaceutically acceptable salts thereof.

7. Compound of Claim 5 wherein $R^1$ is 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinol-7-yl; and pharmaceutically acceptable salts thereof.

8. (Canceled)

9. (Canceled).

10. Compound of Claim 2 wherein $R^2$ is selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, oxo, dimethylamino, aminosulfonyl, cyclopropyl, cyano, hydroxymethyl, nitro, propenyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, morpholinylethylamino, propynyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl;
and pharmaceutically acceptable salts thereof.

11. Compound of Claim 10 wherein $R^2$ is H; and pharmaceutically acceptable salts thereof.

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. Compound of Claim 2 wherein R is selected from (4-pyridyl)-$CH_2$-, (4-pyrimidinyl)-$CH_2$-, (5-pyrimidinyl)-$CH_2$-, (6-pyrimidinyl)-$CH_2$-, (4-pyridazinyl)-$CH_2$- and (6-pyridazinyl)-$CH_2$-; wherein R is unsubstituted or substituted with one or more substituents selected from chloro, fluoro, amino, methylamino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy; and pharmaceutically acceptable salts thereof.

18. (Canceled)

19. Compound of Claim 2 wherein R is selected from (4-pyridyl)-$CH_2$-, (2-methylamino-4-pyrimidinyl)-$CH_2$-, (4-pyridazinyl)-$CH_2$-, , (2-methoxy-4-pyridyl)-$CH_2$-, (4-pyridazinyl)-$CH_2$-, and (2-amino-4-pyrimidinyl)-$CH_2$-; and pharmaceutically acceptable salts thereof.

20. Compound of Claim 2 wherein $R^3$ is selected from unsubstituted or substituted 6-membered nitrogen-containing heteroaryl; and wherein substituted $R^3$ is substituted with one or more substituents independently selected from halo, amino, $C_{1-3}$-alkoxy, hydroxyl, $C_{1-3}$-alkyl and $C_{1-2}$-haloalkyl; and pharmaceutically acceptable salts thereof.

21. (Canceled).

22. (Canceled).

23. Compound of Claim 2 wherein $R^5$ is selected from H, piperidinylethyl and methoxyethoxyethyl; wherein $R^a$ is H; and wherein $R^b$ and $R^c$ are independently selected from H and trifluoromethyl; and pharmaceutically acceptable salts thereof.

24. Compound of Claim 2 wherein R is (4-pyridyl)-$CH_2$-; and pharmaceutically acceptable salts thereof.

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Canceled).

29. Compound of Claim 2 wherein $R^2$ is H or fluoro; and pharmaceutically acceptable salts thereof.

30. A Compound of Claim 2 and pharmaceutically acceptable salts thereof selected from
N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide;
N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide;
N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(2-methylamino-pyrimidin-4-ylmethyl)-amino]-benzamide;
(*R*)-N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[1-(2-methylamino-pyrimidin-4-yl)-ethylamino]-benzamide;
N-(1-Ethyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide;
N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-benzamide;
N-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(1-oxy-pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-fluoro-6-[(2-methoxy-pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-3-fluoro-6-[(2-methoxy-pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-2-[(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(pyridazin-4-ylmethyl)-amino]-benzamide;

2-[1-(2-Amino-pyrimidin-4-yl)-ethylamino]-N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[1-(2-methylamino-pyrimidin-4-yl)-ethylamino]-benzamide; and

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-4-fluoro-6-[(2-methoxy-pyridin-4-ylmethyl)-amino]-benzamide.

31. Compound of Claim 2, and pharmaceutically acceptable salts thereof, comprising N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide.

32. Compound of Claim 2, and pharmaceutically acceptable salts thereof, comprising N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide.

33. (Canceled)

34. Compound of Claim 2, and pharmaceutically acceptable salts thereof, comprising N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(2-methylamino-pyrimidin-4-ylmethyl)-amino]-benzamide.

35.(Canceled).

36. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of Claim 1.

37. (Canceled).

38. (Canceled).

39. (Canceled).

40. (Canceled).

41. (Canceled).

42. (Canceled).

43. (Canceled).

44. (Canceled).

45. (Canceled).

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

| | |
|---|---|
| In re application of: **Qi Huang, et al.** | Attorney Docket No. **A-817 (US)** |
| Application No.: **10/615,809** | Art Unit No.: **1626** |
| Filed: **July 8, 2003** | Examiner: **Joseph R. Kosack** |
| Title: **SUBSTITUTED ANTHRANILIC AMIDE DERIVATIVES AND METHODS OF USE** | |

## APPEAL BRIEF

Mail Stop: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Applicants herein appeal from the Final Rejection mailed November 14, 2006, in which the Examiner rejected claims 1-3, 5-7, 9-11, 17, 19, 20, 23, 24, 29-31, 34 and 36 of the above-identified application, and objected to claim 32. Applicants filed a Notice of Appeal on February 14, 2007.

### CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being facsimile transmitted to Mail Stop: Appeal Brief-Patents, United States Patent and Trademark Office, (571) 273-8300, on the date shown below:

April 16, 2007 Sushma Sanganeria-Brady
Date Sushma Sanganeria-Brady

## Real Party In Interest

The real party in interest is Amgen, Inc.

## Related Appeals And Interferences

Appellants are aware of no other prior or pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

## Status Of Claims

- Claims 5-7, 30, 31 and 34 stand rejected under 35 U.S.C. § 103.
- Claims 1, 2, 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32, 34 and 36 are objected to.
- Claims 3, 4, 8, 9, 12-16, 18, 21, 22, 25-28, 33 and 35 have been canceled.
- Claims 37-45 have been canceled as being drawn to an unelected invention group — but are properly subject to rejoinder

## Status Of Amendments

As indicated in the Advisory Action (Form PTOL-303, section 7) Appellants' proposed amendments submitted in response to the Final Action have been entered.

## Summary Of Claimed Subject Matter

The present application claims compounds having inhibitory kinase activity (such as VEGF/KDR inhibitory activity) and are thus potentially useful in treating cancer and angiogenisis (see specification at page 26 line 4 to page 30 line 31). Specifically, the specification discloses compounds of Formula I (see specification at page 6 line 4, to

page 15, line 5), as well as compounds of Formula I' (see specification at page 15, line 6, to page 24, line13). Specific compounds of particular interest are identified in the specification at page 24, line 14 to page 26, line 2.

Compounds of Formula I are claimed in independent claim 1 and dependent claim 36. Compounds of Formula I' are claimed in independent claim 2 and dependent claims 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32 and 34.

## Grounds Of Rejection To Be Reviewed On Appeal

(1) The Objection to claims 1, 2, 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32, 34 and 36 is based on an assertion that the claims contain non-elected subject matter. However, an intelligible explanation of this objection has never been clearly set forth. In the Final Action, the Examiner asserted that non-elected subject matter remained within the scope of variable $R^2$ (see Final Action at page 2 lines 15-16, and page 4 lines 1-3). However, as Appellants pointed out in their response to the Final Action, a restriction requirement directed to the scope of variable $R^2$ had never been issued. Thus Appellants requested that the Examiner clarify the nature of the objection (see Response to Final Action at page 15 lines 7-10). The Advisory Action fails to provide any clarification.

(2) Claims 5-7 and 9 stand rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819), Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

(3) Claim 31 stands rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

(4) Claims 30 and 34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176) and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

## Argument

### I. The Entirety of Non-Elected Subject Matter Has Been Removed From the Claims On Appeal

The Examiner objects to claims 1, 2, 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32, 34 and 36 on the asserted basis that the claims contain non-elected subject matter. However, an intelligible explanation of this objection has never been clearly set forth. In the Final Action, the Examiner asserted that non-elected subject matter remained within the scope of variable $R^2$ (see Final Action at page 2 lines 15-16, and page 4 lines 1-3). However, as Appellants pointed out in their response to the Final Action, a restriction requirement directed to the scope of variable $R^2$ had never been issued. Thus Appellants requested that the Examiner clarify the nature of the objection (see Response to Final Action at page 15 lines 7-10). The Advisory Action fails to elaborate on the nature of the objection

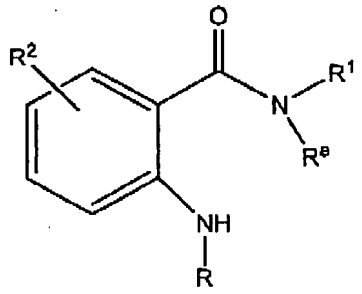
The Examiner's first Restriction Requirement is set forth in the Office Action mailed 12/7/05, in which the Examiner restricted the claimed subject matter between the following two Invention Groups (see 12/7/05 Office Action at page 2 lines 3-17):

I. Claims 1-36, drawn to compounds of Formula I, classified in various subclasses of class 514, 540, 544, 546 548 and 549.

II. Claims 37-45, drawn to drawn to [sic] methods of use of compounds of Formula I, classified in various subclasses of class 514, 540, 544, 546 548 and 549.

The Examiner additionally required that Appellants elect a single compound (see 12/7/05 Office Action at page 3 line 5 to page 6 line 12): In the next Office Action (mailed 4/13/06) the Examiner stated that:

"Pursuant to Applicant's election of species, the scope of the invention will be limited to the following substitutions of the base structure




where:

- R is $-(CH_2)_1-R^3$;
- $R^3$ is a 6 membered ring with ring members consisting of only carbon and nitrogen, optionally substituted as defined, optionally unsaturated as defined;
- All other substituents are as defined."

(4/13/06 Office Action at page 2 line 15 to page 3 line 4)

In response to this Office Action Appellants (1) argued that the proposed restriction of variable $R^3$ was improper as it employed limitation language that found no support in the specification (Appellants additionally proposed that a limitation of $R^3$ to the term "substituted or unsubstituted 5-6 membered heterocyclyl" would be more appropriate); (2) amended the claims to limit the definition of R to $-(CH_2)_1-R^3$; and (3) amended the claims to limit the definition of $R^3$ to "substituted or unsubstituted 5-6 membered heterocyclyl" (See Response mailed 8/11/06 and Response mailed 8/22/06). Appellants subsequently canceled claims 37-45, which were drawn to unelected Invention Group II — subject to the right to rejoinder (see Response to Final Office Action mailed 1/19/07 pages 14-15).

According to the Final Office Action, the Examiner asserts that the claims on appeal retain unelected subject matter within the scope of variable $R^2$. Yet, as shown

above, the Examiner never issued a restriction directed at the scope of variable $R^2$. Appellants' request for clarification on this matter remains unanswered.

While a restriction requirement directed to the scope of $R^2$ was never made, the Examiner did purport to restrict the scope of variables R and $R^3$, as discussed previously above (see 4/13/06 Office Action at page 2 line 15 to page 3 line 4). To the extent that the objection is actually based on a perceived requirement that — in order to remove non-elected subject matter — variable $R^3$ must be "*restricted*" to read: "$R^3$ is a 6-membered ring with ring members consisting of only carbon and nitrogen" such a requirement would be improper. In response to the Final Office Action, Appellants petitioned the Commissioner to Withdraw the Finality of the Office Action, asserting that the proposed restriction of variable $R^3$ was improper." In denying Appellants' petition the Commissioner explained: "The examiner's statement which appears to set a limit on the scope of the claims to be examined was meant to inform applicants of the *scope of the search* pertaining to the claims, **not limit the claim scope**." (3/16/07 PETITION DECISION at page 2 lines 24-27) (emphasis added).

Based on the above set of facts, Appellants assert that the entirety of non-elected subject matter has already been removed from the claims pending on appeal, and that the objection to claims 1, 2, 5-7, 10, 11, 17, 19, 20, 23, 24, 29-32, 34 and 36 is improper.

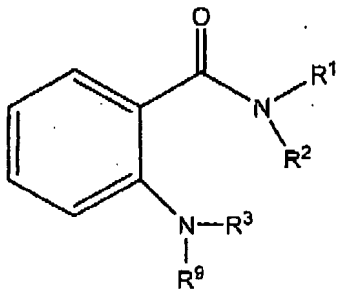
## II. The Examiner Has Failed To Establish A Prima Facie Case Of Obviousness In Relation To Claims 5-7 and 9

The Examiner has rejected claims 5-7 and 9 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819), Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137)*.

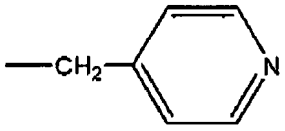
* Appellants question the inclusion of judicial decisions, such as In re Wood, as prior art references. While the holdings of judicial precedent can certainly be relied upon to support the underlying rationale of a rejection, the judicial decision itself does not appear to be properly categorized as "prior art".

Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 5 line 7, to page 7 line 12. Specifically, in attempting to support the rejection the Examiner notes that examples 2.39 and 2.56 of Huth et al. disclose compounds of the formula



where $R^2$ and $R^9$ are hydrogen, $R^3$ is



, and $R^1$ is indol-5-yl, or 4-chloropyridyl. Then the Examiner asserts that:

> "Patani et al. teach ring replacements of NH for $CH_2$ in aromatic and aliphatic rings. See pages 3158-3159. This would make the 5-yl and 6-yl indoles, as well as quinoline/isoquinoline, equivalent structures."

(Final Office Action at page 6 lines 12-14). The Examiner then proceeds to assert that:

> "Fotouhi et al. teach that substituting and [sic] 2,3-dihydro-1H-indole for indole give [sic] molecules with the same utility and comparable activities. See Example 315 on page 109, Example 38 on page 110, and the activities on page 136, column 2."

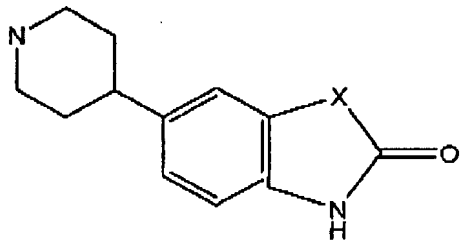
(Final Office Action at page 6 lines 15-17). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teachings of both Patani and Fotouhi far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that

***any*** and all "replacements of NH for $CH_2$ in aromatic and aliphatic rings"† will ***always*** provide "equivalent" structures, with "equivalent" properties relative to ***any and all*** biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad over-arching trends across diverse scaffolds and biologic targets, as a vain attempt in oversimplificaiton.

The Examiner's ultimate conclusion that Patani et all establish the equivalency of all 5-yl and 6-yl indoles under all circumstances is not even supported by the cited text of the reference (i..e., page 3158-3159). A review of the actually cited pages reveals a disclosure of 2 separate chemical scaffolds that both employ certain **5-yl** indolinone-type fragments (see e.g., Figure 34 (compound 52), and Figure 36). Each of these compound is distinct in both structure and chemical activity.

The first cited scaffold in Patani (Figure 34, compound 52) discloses a genus of **PDE III modulators** of the following formula::




X = $CH_2$, NH

This genus covers both

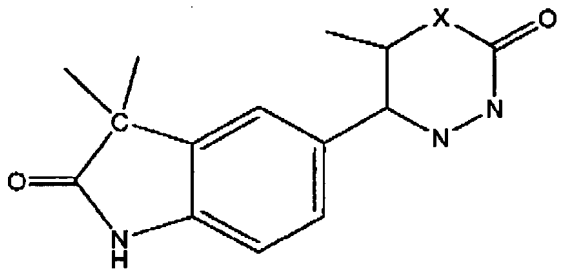
(1) **piperadin-5-yl**, 2,3-dihydro benzimidazol**ones**; and

(2) **piperadin-5-yl**, indoline -2-**one**

The cited scaffold thus encompasses only **5-yl** substituted 2,3-dihydrobenzimidazol**ones**/ or indolin**ones**

† Appellants note this NH could not be substituted with $CH_2$ in aromatic systems without violating rules of valancy.

The second cited scaffold in Patani (Figure 36, compound 54) disclose a genus of **Cardiotonic agents** of the following formula:




Like the previously cited scaffold, this second scaffold also encompasses only **5-yl** substitied 2,3-dihydrobenzimidazol**ones**/ or indolin**ones**

As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

- In making the broad conclusion the Examiner apparently sees fit to discount any activity effects that might be attributable to the differing specific substituents at the 5 position of the cited scaffolds in Patani.
- The cited compounds are all 5-yl substituted indolin**one** compounds. The Examiner does not provide any rational for the implicit equation of indoles and indolinones.
- Contrary to the Examiner's position, the cited reference does not disclose any purported equivalency between either 5-yl or 6-yl indoles. Indeed, the reverence only discloses 5-yl substituted indolinones. How the Examiner now draws a conclusion as to the universal equivalency of any and all corresponding 6-yl isomers, is beyond Appellants comprehension.
- The Examiner does not explain how Patani's disclosure of certain PDE III modulators in Figure 34, and other structurally distinct Cardiotonic agents in Figure 36, would lead any person of skill in

> the art to reasonably expect that certain fragments of the scaffold could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

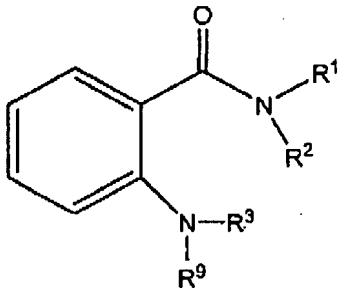
Moreover, the Examiner has not explained how a person of skill in the art, reviewing Fotouhi's disclosure (which relates to ICAM inhibitors of a structurally distinct scaffold), would conclude that the substitution of 2,3, dihydro-1-H indole for indole -- on the completely different kinase inhibitor scaffold covered by the claims on appeal -- would be expected to yield compounds of similar properties. The Advisory Action indicates that this rejection has been maintained because:

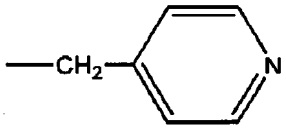
> "Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

**First:** Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets that VEGF/KDR (e.g., PDE III modulators, Cardiotonic agents and ICAM inhibitors)

## III. The Examiner Has Failed To Establish A Prima Facie Case Of Obviousness In Relation To Claim 31

The Examiner has rejected claim 31 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176), Fotouhi et al. (US 2002/0052512 and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 10 line 3, to page 11 line 12. Specifically, in attempting to support the rejection the Examiner notes that example 2.56 of Huth et al. discloses a compound of the formula 

where $R^2$ and $R^9$ are hydrogen, $R^3$ is 

, and $R^1$ is indol-5-yl. Then the Examiner asserts that:

> "Patani et al. teach ring replacements of NH for $CH_2$ in aromatic and aliphatic rings. See pages 3158-3159. This would make the 5-yl and 6-yl indoles equivalent structures."

(Final Office Action at page 10 lines 17-19). The Examiner then proceeds to assert that:

> "Fotouhi et al. teach that substituting and [sic] 2,3-dihydro-1H-indole for indole give [sic] molecules with the same utility and comparable activities. See Example 315 on page 109, Example 38 on page 110, and the activities on page 136, column 2."

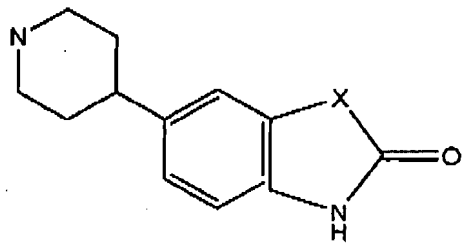
(Final Office Action at page 11 lines 1-3). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teachings of both Patani and Fotouhi far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that ***any*** and all "replacements of NH for $CH_2$ in aromatic and aliphatic rings" will ***always*** provide "equivalent" structures, with "equivalent" properties relative to ***any and all*** biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad over-

arching trends across diverse scaffolds and biologic targets, as a vain attempt in oversimplificaiton.

The Examiner's ultimate conclusion that Patani et all establish the equivalency of all 5-yl and 6-yl indoles under all circumstances is not even supported by the cited text of the reference (i..e., page 3158-3159). A review of the actually cited pages reveals a disclosure of 2 separate chemical scaffolds that both employ certain **5-yl** indolinone-type fragments (see e.g., Figure 34 (compound 52), and Figure 36). Each of these compound is distinct in both structure and chemical activity.

The first cited scaffold in Patani (Figure 34, compound 52) discloses a genus of **PDE III modulators** of the following formula::




$X = CH_2, NH$

This genus covers both

(1) **piperadin-5-yl**, 2,3-dihydro benzimidazol**ones**; and

(2) **piperadin-5-yl**, indoline -2-**one**

The cited scaffold thus encompasses only **5-yl** substited 2,3-dihydrobenzimidazol**ones**/ or indolin**ones**

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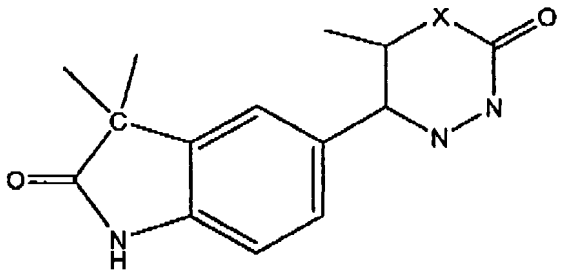



Like the previously cited scaffold, this second scaffold also encompasses only **5-yl** substituted 2,3-dihydrobenzimidazol**ones**/ or indolin**ones**

As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

- In making the broad conclusion the Examiner apparently sees fit to discount any activity effects that might be attributable to the differing specific substituents at the 5 position of the cited scaffolds in Patani.
- The cited compounds are all 5-yl substituted **indolinone** compounds. The Examiner does not provide any rational for the implicit equation of indoles and indolinones.
- Contrary to the Examiner's position, the cited reference does not disclose any purported equivalency between either 5-yl or 6-yl indoles. Indeed, the reverence only discloses 5-yl substituted indolinones. How the Examiner now draws a conclusion as to the universal equivalency of any and all corresponding 6-yl isomers, is beyond Appellants comprehension.
- The Examiner does not explain how Patani's disclosure of certain PDE III modulators in Figure 34, and other structurally distinct Cardiotonic agents in Figure 36, would lead any person of skill in the art to reasonably expect that certain fragments of the scaffold could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

Moreover, the Examiner has not explained how a person of skill in the art, reviewing Fotouhi's disclosure (which relates to ICAM inhibitors of a structurally distinct scaffold), would conclude that the substitution of 2,3, dihydro-1-H indole for indole -- on the completely different kinase inhibitor scaffold covered by the claims on appeal -- would be expected to yield compounds of similar properties. The Advisory Action indicates that this rejection has been maintained because:

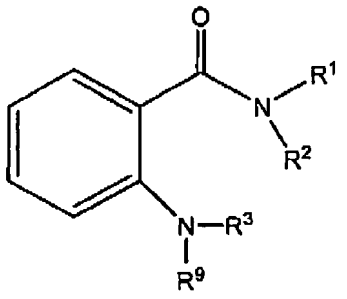
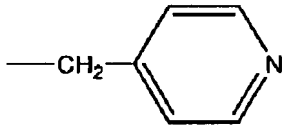
> "Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

**First:** Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets that VEGF/KDR (e.g., PDE III modulators, Cardiotonic agents and ICAM inhibitors)

## IV. The Examiner Has Failed To Establish A Prima Facie Case Of Obviousness In Relation To Claims 30 and 34

The Examiner has rejected claim 30 and 34 under 35 U.S.C. § 103 as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (Chem. Rev. 1996, 3147-3176) and In re Wood (199 USPQ 137). Appellants assert that the Examiner has failed to establish a prima facie case of obviousness.

The Examiner provides an explanation of the basis for the rejection within the Final Office Action at page 8 line 11, to page 9 line 19. Specifically, in attempting to

support the rejection the Examiner notes that example 2.49 of Huth et al. discloses a compound of the formula  where $R^2$ and $R^9$ are hydrogen, $R^3$ is  , and $R^1$ is 7-1,2,3,4-tetrahydroquinolyl. Then the Examiner asserts that:

> "Patani et al. teach ring replacements of NH for $CH_2$ in aromatic and aliphatic rings. See pages 3158-3159. This would make pyridine/pyrimidine, as well as quinoline/isoquinoline equivalent structures."

(Final Office Action at page 9 lines 9-11). The Examiner then notes that hydrogen and methyl would be considered obvious variants under the holding of In re Wood.

Appellants assert that in comparing the prior art against the claimed invention the Examiner interprets the teaching of both Patani far more broadly than is appropriate. To assert, as done here by the Examiner, that Patani broadly teaches that ***any*** and all "replacements of NH for $CH_2$ in aromatic and aliphatic rings" will ***always*** provide "equivalent" structures, with "equivalent" properties relative to ***any and all*** biologic targets, finds absolutely no support within a fair reading of the reference. Indeed a person of skill in the art would recognize such attempts to draw broad over-arching trends across diverse scaffolds and biologic targets, as a vain attempt in oversimplificaiton.

The Examiner's ultimate conclusion that Patani et all establish the equivalency of all pyridine/pyrimidine and quinoline/isoquinoline under all circumstances is not even supported by the cited text of the reference (i..e., page 3158-3159). A review of the

actually cited pages reveals that (1) while some diverse scaffolds do employ pyridine fragments no chemical scaffolds are disclosed that employ pyrimidine fragments; and (2) while one scaffold discloses a specific antibacterial scaffold employing certain quinol**one**.and isoquinol**one** fragments, the references discloses no scaffolds encompassing quinol**ine** and isoquinol**ine** fragments. How the Examiner makes the logical leap establishing the equivalency of quinolones/quinolines and isoquinolones/isoquinonlins, is beyond Appellants' comprehension.

As is readily apparent, there are a number of significant logical gaps between this cited disclosure and the extremely broad interpretation afforded by the Examiner:

- In making the broad conclusion the Examiner apparently sees fit to discount any activity effects that might be attributable to the differing specific substituents required in the cited scaffolds in Patani.
- The cited compound only disclose specific quinolone and isoquinolone compounds. The Examiner does not provide any rational for the implicit equation of these compounds to the structurally distinct quinoline and isoquinoline compounds covered in the claims pending on appeal.
- The Examiner does not explain how Patani's discosure of certain antibacterial quinolones and isoquinolones, would lead any person of skill in the art to reasonably expect that quinoline and isoquinoline fragments employed in the distinct the scaffold covered in the claims on appeal could prove useful in the search for kinase inhibitors, such as inhibitors of VEGF/KDR.

The Advisory Action indicates that this rejection has been maintained because:

> "Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

**First:** Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets that VEGF/KDR (e.g. antibacterial agents)

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> "Applicant has not provided evidence of the biosteric changes not working, and the base compounds being modified by the 103(a) rejection are of similar structure and have the same utility" (See Form PTO-303 Continuation Sheet).

**First:** Appellants stress that the Examiner has improperly placed a burden on them to rebut a case that has not been properly supported in the first instance. Until the Examiner presents a properly supported prima facie case of unpatentability under section 103, there is no need for an applicant to present evidence to rebut the Examiner. **Second:** The Examiner incorrectly asserts that the cited prior art compounds are of similar structure and have the same utility. All of these compounds are designed to affect different targets that VEGF/KDR (e.g., PDE III modulators, Cardiotonic agents and ICAM inhibitors).

## V. The Teaching of Patani

Applicants respectfully submit that the Examiner has interpreted the teaching of Patani et al. far to broadly, and that a fair consideration of this reference does not actually provide anywhere near the absolute concrete guidance on equivalency that has been proposed by the Examiner. Indeed, a review of the pages of Patani et al. specifically cited by Examiner reveals that this disclosure does not even encompass topics such as the substitution of pyrimidine for pyridine, or the substitution of isoquinoline for quinoline. Rather, these pages disclose, *at best*, that:

(1) in relation to antihistamine effect, certain pyridines and phenyls can be employed to obtain active compounds (see Figure 31 at p. 3158),

(2) in relation to antibacterial effect, certain quinilones and isoquinolones can be employed to obtain active compounds (see Figure 38 at p. 3159); and

(3) in relation to certain PDE III modulator scaffolds certain 2,3-dihydrobenzimidazolone fragments can be substituted for indolinone fragments.

The other ring systems discussed at pages 3158-3159 of Patani et al., do not even approach structural similarity between pyridines/pyrimidones or quinolines/isoquinolines. The Examiner's belief that this disclosure of Patani et al. clearly establishes that any substitution of N for CH in any aromatic systems (or NH for $CH_2$ in any non-aromatic systems) will always result in compounds of equivalent activity in all targets, is simply an overreaching interpretation that is not supported by the disclosure itself. Indeed Patani et al. specifically note that:

- "The concept of bioisoseterism is often considered to be qualitative and intuitive." (Patani et al. at page 3147), rather than the facile, precise, all-encompassing generalizations than have been put forth by the Examiner.

- The substitutions discussed in the reference only represent *potential* for producing compounds of similar activity. (See page 3148: "Thus, an additional objective of this review was to demonstrate *the opportunities* that one has in employing bioisosteres" (emphasis added); and "Bioisosteric replacements of functional groups ... have enhanced *the potential* for the successful development of new clinical agents" (emphasis added); See also page 3158: "Classical isosteric substitutions when applied within ring systems result in different heterocyclic analogues which *can be* effective bioisoteres."). Thus, it is clear that Patani et al. do not

purport to endorse the type of broad interpretation that has been set forth by the Examiner, in an attempt to support this rejection. At best, Patani et al. provide a suggestion **to try** isosteric substitutions in order to find bioisosteric equivalents in relation to certain targets. Patani, et al. do not even attempt to suggest that such substitutions will always work in any target at issue.

The Examiner's extremely overbroad interpretation of Patani et al. represents the very foundation of the obviousness rejections. The failure of the Patani reference to actually suggest the propositions set forth by the Examiner, dooms the remainder of the analysis to failure.

## CONCLUSION

Based on the above observations and arguments, Appellants respectfully request that the Board reverse the Objections and Rejections that have been set forth in the Advisory Action and remand the case to the Examiner to pass the claims to allowance.

Respectfully submitted,

Dated: April 16, 2007

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Attorney for Applicants
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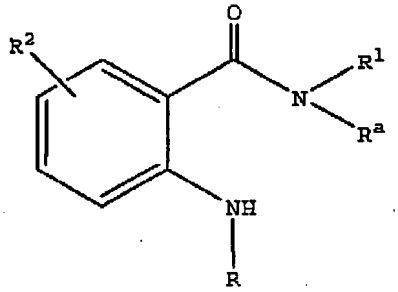
1120 Veterans Boulevard
South San Francisco, CA 94080
Phone: (650) 244-2261
Fax: (650) 837-9422

## CLAIMS APPENDIX

1. A compound of Formula I



I

wherein R is

$-(CH_2)_1-R^3$;

wherein $R^1$ is selected from 1,2-dihydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, 2,3-dihydro-1H-indolyl, and 1,4-benzodioxanyl; wherein $R^1$ is unsubstituted or substituted with one or more substituents selected from bromo, chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, oxo, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-

butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy, methoxy and ethoxy;

wherein $R^2$ is one or more substituents independently selected from

H,

halo,

hydroxy,

amino,

$C_{1-6}$-alkyl,

$C_{1-6}$-haloalkyl,

$C_{1-6}$-alkoxy,

$C_{1-2}$-alkylamino,

aminosulfonyl,

$C_{3-6}$-cycloalkyl,

cyano,

$C_{1-2}$-hydroxyalkyl,

nitro,

$C_{2-3}$-alkenyl,

$C_{2-3}$-alkynyl,

$C_{1-6}$-haloalkoxy,

$C_{1-6}$-carboxyalkyl,

4-6-membered heterocyclyl-$C_{1-6}$-alkylamino,

unsubstituted or substituted phenyl and

unsubstituted or substituted 4-6 membered heterocyclyl;

wherein $R^3$ is substituted or unsubstituted 5-6 membered heterocyclyl; wherein substituted $R^3$ is substituted with one or more substituents independently selected from halo, $-OR^4$, $-SR^4$, $-SO_2R^4$, $-CO_2R^4$, $-CONR^4R^4$, $-COR^4$, $-NR^4R^4$, $-SO_2NR^4R^4$, $-NR^4C(O)OR^4$, $-NR^4C(O)R^4$, cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, lower alkyl substituted with $R^2$, cyano, nitro, lower alkenyl and lower alkynyl;

wherein $R^4$ is independently selected from H, lower alkyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted $C_3$-$C_6$ cycloalkyl, phenyl-$C_{1-6}$-alkyl, optionally substituted 4-6 membered heterocyclyl-$C_{1-6}$-alkyl, and lower haloalkyl;

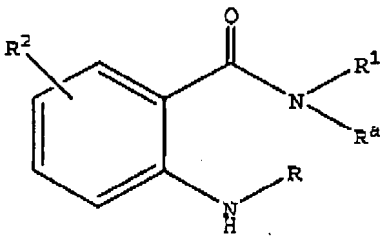
wherein $R^5$ is selected from H, $C_{1-3}$-alkyl, optionally substituted phenyl, optionally substituted phenyl-$C_{1-3}$-alkyl, 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-$C_1$.$C_3$-alkyl, $C_{1-3}$-alkoxy-$C_{1-2}$-alkyl and $C_{1-3}$-alkoxy-$C_{1-3}$-alkoxy-$C_{1-3}$-alkyl;

wherein $R^a$ is selected from H and $C_{1-2}$-alkyl; and

wherein $R^b$ and $R^c$ are independently selected from H and $C_{1-2}$-haloalkyl;

and pharmaceutically acceptable salts thereof.

2. A compound of Formula I'



I'

wherein R is

$-(CH_2)_1-R^3$;

wherein $R^1$ is selected from 1,2-dihydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, 2,3-dihydro-1H-indolyl, and 1,4-benzodioxanyl; wherein $R^1$ is unsubstituted or substituted with one or more substituents selected from bromo, chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, oxo, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-

methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy, methoxy and ethoxy;;

wherein $R^2$ is one or more substituents independently selected from

H,

halo,

hydroxy,

amino,

$C_{1-6}$-alkyl,

$C_{1-6}$-haloalkyl,

$C_{1-6}$-alkoxy,

$C_{1-2}$-alkylamino,

aminosulfonyl,

$C_{3-6}$-cycloalkyl,

cyano,

$C_{1-2}$-hydroxyalkyl,

nitro,

$C_{2-3}$-alkenyl,

$C_{2-3}$-alkynyl,

$C_{1-6}$-haloalkoxy,

$C_{1-6}$-carboxyalkyl,

4-6-membered heterocyclyl-$C_{1-6}$-alkylamino,

unsubstituted or substituted phenyl and

unsubstituted or substituted 4-6 membered heterocyclyl;

wherein $R^3$ is substituted or unsubstituted 5-6 membered heterocyclyl; wherein substituted $R^3$ is substituted with one or more substituents independently selected from halo, $-OR^4$, $-SR^4$, $-SO_2R^4$, $-CO_2R^4$, $-CONR^4R^4$, $-COR^4$, $-NR^4R^4$, $-SO_2NR^4R^4$, $-NR^4C(O)OR^4$, $-NR^4C(O)R^4$, cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, lower alkyl substituted with $R^6$, cyano, nitro, lower alkenyl and lower alkynyl;

wherein $R^4$ is independently selected from H, lower alkyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted $C_3$-$C_6$ cycloalkyl, phenyl-$C_{1-6}$-alkyl, optionally substituted 4-6 membered heterocyclyl-$C_{1-6}$-alkyl, and lower haloalkyl;

wherein $R^5$ is selected from H, $C_{1-3}$-alkyl, optionally substituted phenyl, optionally substituted phenyl-$C_{1-3}$-alkyl, 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-$C_1$-$C_3$-alkyl, $C_{1-3}$-alkoxy-$C_{1-2}$-alkyl and $C_{1-3}$-alkoxy-$C_{1-3}$-alkoxy-$C_{1-3}$-alkyl;

wherein $R^6$ is selected from H, halo, hydroxy, amino, $C_{1-6}$-alkoxy, $C_{1-2}$-alkylamino, aminosulfonyl, $C_{3-6}$-cycloalkyl, cyano, nitro, $C_{1-6}$-haloalkoxy, carboxy, 4-6-membered heterocyclyl-$C_{1-6}$-alkylamino, unsubstituted or substituted phenyl and unsubstituted or substituted 4-6 membered heterocyclyl;

wherein $R^a$ is selected from H and $C_{1-2}$-alkyl; and

wherein $R^b$ and $R^c$ are independently selected from H and $C_{1-2}$-haloalkyl;

and pharmaceutically acceptable salts thereof.

3. (Canceled)

4. (Canceled)

5. Compound of Claim 2 wherein $R^1$ is selected from 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinol-7-yl, 2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinol-7-yl, 2,3-dihydro-1H-indolyl, 3,3-dimethyl-2,3-dihydro-1H-indol-6-yl, 1-ethyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl, and 1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl; and pharmaceutically acceptable salts thereof.

6. Compound of Claim 5 wherein $R^1$ is 3,3-dimethyl-2,3-dihydro-1H-indol-6-yl; and pharmaceutically acceptable salts thereof.

7. Compound of Claim 5 wherein $R^1$ is 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinol-7-yl; and pharmaceutically acceptable salts thereof.

8. (Canceled)

9. (Canceled).

10. Compound of Claim 2 wherein $R^2$ is selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, oxo, dimethylamino, aminosulfonyl, cyclopropyl, cyano, hydroxymethyl, nitro, propenyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl; morpholinylethylamino, propynyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl;
and pharmaceutically acceptable salts thereof.

11. Compound of Claim 10 wherein $R^2$ is H; and pharmaceutically acceptable salts thereof.

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. Compound of Claim 2 wherein R is selected from (4-pyridyl)-$CH_2$-, (4-pyrimidinyl)-$CH_2$-, (5-pyrimidinyl)-$CH_2$-, (6-pyrimidinyl)-$CH_2$-, (4-pyridazinyl)-$CH_2$- and (6-pyridazinyl)-$CH_2$-; wherein R is unsubstituted or substituted with one or more substituents selected from chloro, fluoro, amino, methylamino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy; and pharmaceutically acceptable salts thereof.

18. (Canceled)

19. Compound of Claim 2 wherein R is selected from (4-pyridyl)-$CH_2$-, (2-methylamino-4-pyrimidinyl)-$CH_2$-, (4-pyridazinyl)-$CH_2$-, , (2-methoxy-4-pyridyl)-$CH_2$-, (4-pyridazinyl)-$CH_2$-, and (2-amino-4-pyrimidinyl)-$CH_2$-; and pharmaceutically acceptable salts thereof.

20. Compound of Claim 2 wherein $R^3$ is selected from unsubstituted or substituted 6-membered nitrogen-containing heteroaryl; and wherein substituted $R^3$ is substituted with one or more substituents independently selected from halo, amino, $C_{1-3}$-alkoxy, hydroxyl, $C_{1-3}$-alkyl and $C_{1-2}$-haloalkyl; and pharmaceutically acceptable salts thereof.

21. (Canceled).

22. (Canceled).

23. Compound of Claim 2 wherein $R^5$ is selected from H, piperidinylethyl and methoxyethoxyethyl; wherein $R^a$ is H; and wherein $R^b$ and $R^c$ are independently selected from H and trifluoromethyl; and pharmaceutically acceptable salts thereof.

24. Compound of Claim 2 wherein R is (4-pyridyl)-$CH_2$-; and pharmaceutically acceptable salts thereof.

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Canceled).

29. Compound of Claim 2 wherein $R^2$ is H or fluoro; and pharmaceutically acceptable salts thereof.

30. A Compound of Claim 2 and pharmaceutically acceptable salts thereof selected from

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide;

N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(2-methylamino-pyrimidin-4-ylmethyl)-amino]-benzamide;

(*R*)-N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[1-(2-methylamino-pyrimidin-4-yl)-ethylamino]-benzamide;

N-(1-Ethyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-benzamide;

N-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(1-oxy-pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-fluoro-6-[(2-methoxy-pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-3-fluoro-6-[(2-methoxy-pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-2-[(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(pyridazin-4-ylmethyl)-amino]-benzamide;

2-[1-(2-Amino-pyrimidin-4-yl)-ethylamino]-N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[1-(2-methylamino-pyrimidin-4-yl)-ethylamino]-benzamide; and

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-4-fluoro-6-[(2-methoxy-pyridin-4-ylmethyl)-amino]-benzamide.

31. Compound of Claim 2, and pharmaceutically acceptable salts thereof, comprising N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide.

32. Compound of Claim 2, and pharmaceutically acceptable salts thereof, comprising N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide.

33. (Canceled)

34. Compound of Claim 2, and pharmaceutically acceptable salts thereof, comprising N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(2-methylamino-pyrimidin-4-ylmethyl)-amino]-benzamide.

35.(Canceled).

36. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of Claim 1.

37. (Canceled).

38. (Canceled).

39. (Canceled).

40. (Canceled).

41. (Canceled).

42. (Canceled).

43. (Canceled).

44. (Canceled).

45. (Canceled).